Total Synthesis of the Formamycin Aglycon, Formamycinone

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SUPPORTING INFORMATION

Experimental procedures for synthesis of compounds **8** to **16**; Stereochemical assignments for compounds **9** and **22**; and comparison of the ^1H -NMR and ^{13}C -NMR data of formamycin and formamycin aglycon (25 pages). This material is available free of charge via the Internet at <http://pubs.acs.org>.

General. All reactions were conducted in flame-dried glassware under nitrogen. All solvents were purified before use. THF and Et₂O were dried by distillation from sodium benzophenone ketyl, or used as is from a solvent purification system (Anhydrous Engineering)¹. CH₂Cl₂ was dried by distillation from CaH₂, or used as is from a solvent purification system (Anhydrous Engineering). Pyridine and 2,6-lutidine were dried by distillation from CaH₂. Methanol was distilled from magnesium turnings. Toluene was dried by distillation from sodium. All other commercially available reagents and solvents were used as received. 4Å molecular sieves were flame-dried under vacuum just prior to use.

¹H NMR data were recorded at either 500 MHz or 400 MHz using a Varian I-500 or a Varian XL-400 instrument respectively. ¹H NMR chemical shifts are reported relative to residual CHCl₃ (7.26 ppm). ¹³C NMR data were recorded at either 125 MHz or 100 MHz using a Varian I-500 or a Varian XL-400 instrument respectively. ¹³C chemical shifts are reported relative to the central line of CDCl₃ (77.0 ppm). Infrared spectra were recorded using a Perkin Elmer Spectrum 1000 FT-IR (thin film). High resolution mass spectroscopy were performed on a VG 70-250-S Micromass, Inc. mass spectrometer at the University of Michigan Mass Spectrometry Laboratory. Optical rotations were measured on a Rudolph Autopol III polarimeter using a 1 mL capacity quartz cell with a 10 cm path length. Elemental analyses were performed by the Elemental Analysis Laboratory at the University of Michigan.

Chromatographic purifications were performed using Kieselgel 60, 230-400 mesh, silica gel unless indicated otherwise. All compounds purified by chromatography

¹ Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organomet.* **1996**, *15*, 1518.

were sufficiently pure for use in further experiments, unless indicated otherwise. Analytical and semi-preparative HPLC normal phase separations were performed using an HPLC system composed of two Rainin HPXL pumps, a Rheodyne 7125 injector, a Dynamax UV-C or RI-1 detector and Dynamax software on a Macintosh II SI to integrate the peaks. CuTC,² Ph₂P(O)OBu₄N³ and (*E*)-ethyl-β-iodoacrylate⁴ were prepared according to literature procedures.

Synthesis of (4*R*) 4-Benzyl-3-[2-(1'*S*,2*R*,4*E*)-(1'-methoxymethoxy-hexyl)-4-methyl-5-(trimethylsilyl)-pent-4-enoyl]-oxazolidin-2-one (20). To a solution of **7** (15.7 g, 35.3 mmol) and *i*-Pr₂NEt (18.5 mL, 105.8 mmol, 3 eq.) in CH₂Cl₂ (7.5 mL) at 0 °C was added dropwise MOMCl (7.7 mL, 101.0 mmol, 2.9 eq.). After 1.5 h at 0 °C, the reaction mixture was diluted with brine and the aqueous layer extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered and concentrated. The crude residue was taken up in cold hexanes (0 °C), filtered through a pad of celite and rinsed thoroughly with hexanes. After concentration, **20** was obtained as a yellow oil which was used directly in the next step.

Purification of an aliquot by flash chromatography on silica gel (hexanes / ethyl acetate = 85/15) afforded **20** as a colorless oil having the following properties: ¹H NMR

² Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.

³ Srogl, J.; Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 12376.

⁴ Dixon, D. J.; Ley, S. V.; Longbottom, D. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2231; Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, 29, 1475.

(500 MHz, CDCl_3) δ 7.35-7.32 (2H), 7.29-7.26 (1H), 7.22 (d, J = 6.8 Hz, 2H), 5.27 (s, 1H), 4.71 (dd, J = 7.1 Hz, 1H), 4.65 (ddd, J = 10.0, 6.6 and 2.9 Hz, 1H), 4.54 (d, J = 7.1 Hz, 1H), 4.50 (dt, J = 8.8 and 4.4 Hz, 1H), 4.09-4.03 (2H), 3.76 (ddd, J = 8.3, 4.1 and 4.1 Hz, 1H), 3.37 (s, 3H), 3.32 (dd, J = 13.8 and 3.0 Hz, 1H), 2.65 (dd, J = 14.3 and 10.4 Hz, 1H), 2.57 (dd, J = 13.2 and 10.4 Hz, 1H), 2.32 (dd, J = 13.8 and 3.8 Hz, 1H), 1.86 (s, 3H), 1.64-1.47 (3H), 1.33-1.26 (5H), 0.89 (t, J = 6.8 Hz, 3H), 0.1 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.6, 153.2, 152.1, 135.5, 129.3, 128.9, 127.3, 125.3, 96.1, 78.8, 65.7, 56.0, 44.0, 40.6, 37.9, 32.0, 31.7, 25.6, 22.6, 22.0, 14.0, 0.0; IR (thin film) 2954, 2360, 1783, 1698, 1382, 1247, 1194, 1038, 840, 700 cm^{-1} ; HRMS (FAB) for $\text{C}_{27}\text{H}_{43}\text{O}_5\text{SiNa}$ $[\text{M}+\text{Na}]^+$ calcd. 512.2808, found 512.2816 m/z ; Anal. calcd for $\text{C}_{27}\text{H}_{43}\text{O}_5\text{NSi}$: C, 66.22; H, 8.85; N, 2.86; Found: C, 66.04; H, 9.08; N, 2.49; $[\alpha]_{\text{D}}^{24} = -81.3$ (c 1.55, CHCl_3).

Synthesis of (1'S,2S,4E) 2-(1'-Methoxymethoxy-hexyl)-4-methyl-5-(trimethylsilyl)-pent-4-en-1-ol (8): To a solution of **20** in Et_2O (500 mL) and EtOH (2.45 mL, 42.3 mmol, 1.2 eq.) at 0 °C was added dropwise LiBH_4 (2M solution in THF, 42.3 mmol, 21.2 mL, 1.2 eq.). After 4 hours at 0 °C, the reaction mixture was carefully quenched with an aqueous solution of NaOH (1M, 200 mL) and the solution stirred until clear phases were obtained (1h30). The aqueous layer was extracted with Et_2O , the combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated. Purification of the crude material by flash chromatography on silica gel (hexanes / ethyl acetate = 95/5 to 80/20) afforded 9.60 g (86% from **7**) of **8** as a colorless

oil. ^1H NMR (400 MHz, CDCl_3) δ 5.24 (s, 1H), 4.67 (d, J = 6.8 Hz, 1H), 4.63 (d, J = 6.8 Hz, 1H), 3.65 (m, 1H), 3.63 (m, 1H), 3.55 (m, 1H), 3.40 (s, 3H), 2.81 (m, 1H), 2.11-2.04 (2H), 1.94 (m, 1H), 1.78 (s, 3H), 1.54 (m, 1H), 1.47-1.42 (2H), 1.33-1.24 (5H), 0.88 (t, J = 7.0 Hz, 3H), 0.08 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.8, 126.0, 96.5, 79.6, 63.5, 55.9, 40.6 (2C), 31.8, 30.4, 25.7, 22.6, 21.1, 14.0, -0.1; IR (thin film) 3445, 2954, 2932, 1615, 1247, 1152, 1097, 1040, 861, 837 cm^{-1} ; HRMS (CI, NH_3) for $\text{C}_{17}\text{H}_{36}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ calcd. 317.2512, found 317.2500 m/z ; Anal. calcd for $\text{C}_{17}\text{H}_{36}\text{O}_3\text{Si}$: C, 64.50; H, 11.46; Found: C, 64.81; H, 11.08; $[\alpha]_{\text{D}}^{24} = +20.1$ (c 1.51, CHCl_3).

Synthesis of (1'S,3S,4R,6E) 2-Ethoxy-4-(1'-methoxymethoxy-hexyl)-6-methyl-7-(trimethylsilyl)-hepta-1,6-dien-3-ol (9): To a solution of oxalyl chloride (4.3 mL, 49.6 mmol, 2 eq.) in CH_2Cl_2 (250 mL) at -70°C was added dropwise DMSO (5.3 mL, 74.4 mmol, 3 eq.). After 15 min. at -70°C , a solution of **8** (7.84 g, 24.8 mmol) in CH_2Cl_2 (15 mL) was added slowly via canula. The reaction mixture was stirred for another 15 min at -70°C before addition of Et_3N (13.8 mL, 99.2 mmol, 4 eq.). The reaction mixture was allowed to warm to 0°C over a 35 min. period and then stirred at 0°C for 15 min. 300 mL of cold hexanes were then added and the resulting suspension was filtered through celite, rinse thoroughly with cold hexanes and concentrated to 150 mL. The solution was diluted with water (100 mL), and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated to give a slightly yellow oil which was used directly in the next step without any purification. To a solution of ethylvinyl ether (12 mL, 125 mmol) in

THF (25 mL) at $-70\text{ }^{\circ}\text{C}$ was added *t*-BuLi (1.5 M in pentane, 125 mmol, 83 mL) dropwise such as $T < -60\text{ }^{\circ}\text{C}$. The reaction mixture was then warmed to $0\text{ }^{\circ}\text{C}$, stirred at that temperature for 30 min, cooled to $-70\text{ }^{\circ}\text{C}$ and diluted with THF (50 mL). The solution of α -ethoxyvinyl lithium was further cooled to $-118\text{ }^{\circ}\text{C}$ (internal temperature) and a solution of the above crude aldehyde was then slowly added. After 10 min at $-118\text{ }^{\circ}\text{C}$, the reaction mixture was quenched by slow addition of MeOH (5 mL) followed by an aqueous saturated solution of NaHCO_3 . The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers washed with brine, dried over K_2CO_3 , filtered and concentrated to give a slightly yellow oil. Purification by flash chromatography on silica gel (hexanes / ethyl acetate = 95/5) gave **9** as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 5.28 (s, 1H), 4.65 (s, 2H), 4.27 (t, $J = 3.7\text{ Hz}$, 1H), 4.22 (d, $J = 1.7\text{ Hz}$, 1H), 4.01 (d, $J = 1.7\text{ Hz}$, 1H), 3.78-3.68 (2H), 3.63 (dt, $J = 6.7$ and 2.7 Hz , 1H), 3.38 (s, 3H), 2.70 (d, $J = 4.2\text{ Hz}$, 1H), 2.31 (dd, $J = 13.9$ and 7.6 Hz , 1H), 2.25 (m, 1H), 2.18 (dd, $J = 13.9$ and 7.6 Hz , 1H), 1.75 (s, 3H), 1.62-1.53 (2H), 1.35-1.17 (9H including 1.27 (t, $J = 7.1\text{ Hz}$, 3H)), 0.87 (t, $J = 7.1\text{ Hz}$, 3H), 0.07 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 162.7, 154.9, 124.7, 95.8, 81.7, 81.0, 74.3, 62.7, 55.7, 40.9, 37.0, 31.8, 31.3, 26.0, 22.7, 21.2, 14.4, 14.0, -0.1; IR (thin film) 3468 (br), 2955, 2361, 1662, 1616, 1247, 1100, 1040, 870, 840 cm^{-1} ; HRMS (CI, NH_3) for $\text{C}_{21}\text{H}_{42}\text{O}_4\text{Si}$ $[\text{M}+\text{H}]^+$ calcd. 387.2931, found 387, 2985 m/z ; $[\alpha]_{\text{D}}^{25} = -3.3$ (c 1.04, CHCl_3).

Synthesis of (1'*S*,3*S*,4*R*,6*E*) 2-Ethoxy-3-*p*-methoxybenzyloxy-4-(1'-methoxymethoxy-hexyl)-6-methyl-7-(trimethylsilyl)-hepta-1,6-diene (21): To a $0\text{ }^{\circ}\text{C}$ solution of **9** in

7

layers were washed successively with an aqueous saturated solution of NaHCO₃ and brine, dried over MgSO₄, filtered and concentrated to give 7.05 g (97%) of a **10** as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.21 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 5.20 (s, 1H), 4.62 (d, *J* = 6.6 Hz, 1H), 4.50 (d, *J* = 6.6 Hz, 1H), 4.42 (d, *J* = 11.0 Hz, 1H), 4.27 (d, *J* = 11.0 Hz, 1H), 3.86 (d, *J* = 4.4 Hz, 1H), 3.76 (s, 3H), 3.46 (dt, *J* = 9.2 and 2.9 Hz, 1H), 3.33 (s, 3H), 2.38-2.28 (2H), 2.12 (s, 3H), 2.03 (dd, *J* = 13.4 and 9.0 Hz, 1H), 1.69 (s, 3H), 1.54-1.36 (3H), 1.27-1.14 (5H), 0.84 (t, *J* = 7.0 Hz, 3H), 0.03 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 211.3, 159.3, 152.3, 129.7, 129.4, 129.6, 113.7, 96.2, 84.3, 78.0, 72.1, 55.8, 42.4, 39.8, 31.6, 30.0, 26.5, 26.2, 22.6, 21.0, 14.0, -0.1; IR (thin film) 2954, 1715, 1614, 1515, 1249, 1035, 838 cm⁻¹; HRMS (electrospray) for C₂₇H₄₆O₅SiNa [M+Na]⁺ calcd. 501.3012, found 501.3020; [α]_D²⁵ = -83.0 (*c* 0.43, CHCl₃).

Synthesis of (1'S,4S,5S,6R,8E) 5-*p*-Methoxybenzyloxy-6-(1'-methoxymethoxy-hexyl)-4,8-dimethyl-9-(trimethylsilanyl)-non-8-en-2-yn-4-ol (22**):**

To a solution of **10** (4.3 g, 9.0 mmol) in THF (80 mL) at -45 °C was added 1-propynylmagnesium bromide (0.5 M in THF, 25 mmol, 50 mL, 2.8 eq.). After 12 h at -45 °C, the reaction mixture was allowed to warm to -30 °C and stirred 3 h at that temperature. The reaction was then poured into an aqueous saturated solution of NH₄Cl and the aqueous layer extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered and concentrated. Purification of the crude material by flash chromatography on silica gel (hexanes / ethyl acetate = 85/15 to 70/30) afforded 4.36 g (94%) of **22** as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.27 (d, *J* = 8.8 Hz, 2H),

6.87 (d, $J = 8.8$ Hz, 2H), 5.24 (s, 1H), 4.73 (d, $J = 6.8$ Hz, 1H), 4.70 (d, $J = 10.7$ Hz, 1H), 4.57 (d, $J = 6.8$ Hz, 1H), 4.54 (d, $J = 10.7$ Hz, 1H), 4.30 (s, 1H), 3.80 (s, 3H), 3.66 (m, 1H), 3.45 (d, $J = 5.1$ Hz, 1H), 3.39 (s, 3H), 2.68 (dd, $J = 13.7$ and 3.8 Hz, 1H), 2.56 (m, 1H), 2.00 (dd, $J = 13.7$ and 11.8 Hz, 1H), 1.83 (s, 3H), 1.79 (s, 3H), 1.62-1.47 (5H including 1.52 (s, 3H)), 1.32-1.23 (6H), 0.90 (t, $J = 7.1$ Hz, 3H), 0.10 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 159.1, 153.5, 130.6, 129.3, 129.5, 113.7, 95.2, 83.6, 82.5, 80.2, 77.6, 74.4, 71.6, 55.9, 55.2, 41.1, 40.4, 31.6, 29.6, 27.3, 26.4, 22.7, 20.8, 14.1, 3.8, -0.1; IR (thin film) 3409 (br), 2954, 2252, 1614, 1515, 1456, 1249, 1095, 1036, 869, 840 cm^{-1} ; HRMS (electrospray) for $\text{C}_{30}\text{H}_{50}\text{O}_5\text{SiNa}$ $[\text{M}+\text{Na}]^+$ calcd. 541.3325, found 541.3315; $[\alpha]_{\text{D}}^{25} = -87.9$ (c 0.33, CHCl_3).

Synthesis of (1'S,2E,4S,5S,6R,8E) 2-[(Tributyl)stannyl]-4,8-dimethyl-5-p-methoxybenzyloxy-6-(1'-methoxymethoxy-hexyl)-9-(trimethylsilyl)-nona-2,8-dien-4-ol (11): To a solution of **22** (1g, 1.9 mmol) in THF (3.8 mL) at 23 °C was added $\text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3$ (40 mg, 4% mol.). Bu_3SnH (10.1 mL, 38.5 mmol, 20 eq.) was then added dropwise over 1h30 via a syringe pump addition. After 1h at 23 °C, the reaction mixture was concentrated. Purification of the crude material by flash chromatography on silica gel (hexanes / ethyl acetate = 100/0 to 90 /10) afforded 0.764 g of **11** and 0.490 g of **22**. Resubjection of **22** to the same conditions gave after 2 recycles an additionnal 0.470 g of **11** (79 % after 2 recycles). ^1H NMR (400 MHz, CDCl_3) δ 7.25 (d, $J = 8.6$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 5.73 (d, $J = 1.8$ Hz, $J_{\text{Sn-H}} = 79.7$ Hz, 1H), 5.22 (s, 1H), 4.65 (d, $J = 11.0$ Hz, 1H), 4.64 (d, $J = 6.6$ Hz, 1H), 4.51 (2H), 3.81 (s, 1H), 3.80 (s, 3H), 3.59 (m,

1H), 3.50 (d, $J = 4.8$ Hz, 1H), 3.37 (s, 3H), 2.65 (dd, $J = 13.8$ and 3.7 Hz, 1H), 2.35 (m, 1H), 2.16 (s, $J_{Sn-H} = 24.5$ Hz, 3H), 2.02 (dd, $J = 13.8$ and 11.7 Hz, 1H), 1.77 (s, 3H), 1.59-1.39 (11H), 1.34-1.23 (12H), 0.93-0.80 (18H), 0.09 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.9, 153.7, 144.5, 140.7, 131.0, 128.5, 126.2, 113.6, 95.3, 84.1, 78.7, 78.0, 74.0, 55.8, 55.2, 41.0, 40.2, 31.7, 29.8, 29.2 ($J_{Sn-C} = 19.1$ Hz), 27.4 ($J_{Sn-C} = 54.2$ Hz), 26.5, 22.7, 20.9, 20.7, 14.1, 13.7, 9.2 ($J_{Sn-C} = 309.8$ Hz), -0.1; IR (thin film) 3414, 2955, 1614, 1514, 1250, 1090, 1040, 868, 840 cm^{-1} ; HRMS (electrospray) for $\text{C}_{42}\text{H}_{78}\text{O}_5\text{SiSnNa}$ $[\text{M}+\text{Na}]^+$ calcd. 833.4538, found 833.4570; $[\alpha]_{\text{D}}^{25} = -27.6$ (c 0.54, CHCl_3).

Synthesis of (1'S,2E,4S,5S,6R)-2-[(Tributyl)stannyl]-4-methyl-4,7-O-methylidene-5-*p*-methoxybenzyloxy-6-(*E*-2'-methyl-3'-trimethylsilyl-2'-enyl)

dodec-2-ene (12): To a solution of **11** (0.76 g, 0.94 mmol) and 2,6-di-*t*-butyl-4-methylpyridine (2,6-DTBP) (0.58 g, 2.80 mmol, 3 eq.) in CH_2Cl_2 (18 mL) at -78°C was added Me_2BBr (0.14 mL, 1.40 mmol, 1.5 eq.) dropwise. After 30 min. at -60°C , an additional 0.15 mL of Me_2BBr was added and the stirring was continued for 20 min. The reaction mixture was then poured into an aqueous saturated solution of NaHCO_3 , and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were dried over MgSO_4 , filtered and concentrated. Purification of the crude material by flash chromatography on silica gel (hexanes / ethyl acetate = 100/0 to 100/3) afforded 0.674 g (92%) of **12** as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.24 (d, $J = 8.7$ Hz, 2H), 6.86 (d, $J = 8.7$ Hz, 2H), 5.81 (d, $J = 1.7$ Hz, $J_{Sn-H} = 77.4$ Hz, 1H), 5.33 (s, 1H), 4.92 (d, $J = 6.5$ Hz, 1H), 4.87 (d, $J = 6.5$ Hz, 1H), 4.46 (d, $J = 11.3$ Hz, 1H), 4.43 (d, $J = 11.3$ Hz,

1H), 4.06 (m, 1H), 3.81 (s, 3H), 3.41 (d, $J = 3.9$ Hz, 1H), 2.39 (dd, $J = 13.9$ and 9.0 Hz, 1H), 2.32 (dd, $J = 13.9$ and 5.9 Hz, 1H), 2.17 (m, 1H), 2.00 (d, $J = 2.0$ Hz, $J_{\text{Sn-H}} = 49$ Hz, 3H), 1.75 (s, 3H), 1.65-1.24 (23H), 0.96-0.79 (18H), 0.12 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 159.0, 153.5, 141.8, 140.8, 1309.9, 128.9, 126.4, 113.6, 89.3, 85.5, 83.7, 75.0, 72.9, 55.2, 45.0, 41.1, 32.4, 31.8, 29.2 ($J_{\text{Sn-C}} = 19.7$ Hz), 27.4 ($J_{\text{Sn-C}} = 54.0$ Hz), 26.3, 25.0, 22.6, 21.2, 20.8, 14.1, 13.7, 9.3 ($J_{\text{Sn-C}} = 318.6$ Hz), 0.0; IR (thin film) 2926, 1614, 1514, 1464, 1248, 1040, 865, 840 cm^{-1} ; HRMS (electrospray) for $\text{C}_{41}\text{H}_{74}\text{O}_5\text{SiSnNa}$ $[\text{M}+\text{Na}]^+$ calcd. 801.4276, found 801.4299; $[\alpha]_{\text{D}}^{25} = -39.5$ (c 0.20, CHCl_3).

Synthesis of Methyl-(2*E*,4*E*,6*S*,7*S*,8*R*,9*S*)-4,6-dimethyl-6,9-*O*-methyldiene-8-(*E*-2'-methyl-3'-trimethylsilyl-2'-enyl)-7-*p*-methoxybenzyloxy-tetradeca-2,4-dienoate (13): To a solution of **12** (70 mg, 0.09 mmol), tetrabutyl ammonium diphenylphosphinate (45.5 mg, 0.1 mmol, 1.1 eq.) and CuTC (34 mg, 0.18 mmol, 2 eq.) in NMP (0.5 mL) at 23 °C was added a solution of (*E*)-ethyl β -iodoacrylate (34 mg, 0.16 mmol, 1.8 eq.) in NMP (0.3 mL) over 45 min via a syringe pump addition. After the addition was complete, the reaction mixture was diluted with Et_2O and filtered through neutral alumina. The filtrate was successively washed with water (6 mL) and brine. The organic layer was dried over MgSO_4 , filtered and concentrated. Purification of the crude material by preparative thin layer chromatography (hexanes / ethyl acetate = 90/10) gave 47.4 mg (92%) of **13** as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.23 (d, $J = 8.7$ Hz, 2H), 7.19 (d, $J = 15.8$ Hz, 1H), 6.90 (d, $J = 8.7$ Hz, 2H), 5.82 (d, $J = 15.8$ Hz, 1H), 5.74 (s, 1H), 5.33 (s, 1H), 4.94 (d, $J = 5.9$ Hz, 1H), 4.81 (d, $J = 5.9$ Hz, 1H), 4.56 (d, $J = 11.7$

Hz, 1H), 4.29 (d, $J = 11.7$ Hz, 1H), 4.10 (m, 1H), 3.85 (s, 3H), 3.77 (s, 3H), 3.34 (d, $J = 3.7$ Hz, 1H), 2.40-2.32 (2H), 2.17 (m, 1H), 1.86 (s, 3H), 1.85 (s, 3H), 1.68 (m, 1H), 1.51 (s, 3H), 1.48-1.27 (7H), 0.91 (t, $J = 6.8$ Hz, 3H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 167.8, 159.4, 153.1, 150.8, 144.9, 133.0, 130.1, 129.8, 126.7, 115.6, 113.8, 89.4, 83.5, 82.3, 74.4, 71.8, 55.3, 51.4, 44.4, 40.3, 32.2, 21.7, 26.2, 22.8, 22.6, 21.4, 14.0, 12.8, 0.0; IR (thin film) 2953, 1721, 1619, 1515, 1301, 1249, 1060, 1040, 840 cm^{-1} ; HRMS (electrospray) for $\text{C}_{33}\text{H}_{52}\text{O}_5\text{SiNa}$ $[\text{M}+\text{Na}]^+$ calcd. 595.3431, found 595.3435; $[\alpha]_{\text{D}}^{25} = -63.8$ (c 0.50, CHCl_3).

Synthesis of Methyl-(2*E*,4*E*,6*S*,7*S*,8*R*,9*S*)-4,6-dimethyl-6,9-*O*-methyldiene-8-(*E*-2'-methyl-3'-trimethylsilylanyl-2'-enyl)-7-[(triethylsilyl)oxy]-tetradeca-2,4-dienoate (23**):** To a solution of **13** (29 mg, 0.05 mmol) in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (1 mL/ 0.1 mL) at 0 °C was added DDQ (17.2 mg, 0.08 mmol, 1.5 eq.). After 1h at 0 °C and 1h at 23 °C, the reaction mixture was diluted with an aqueous saturated solution of NaHCO_3 . The aqueous layer was extracted with CH_2Cl_2 , the combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated. The crude material was dissolved in CH_2Cl_2 (0.5 mL) and cooled to 0 °C. 2,6-Lutidine (18 μL , 0.15 mmol, 3 eq.) was then added, followed by TESOTf (23 μL , 0.10 mmol, 2 eq.). After 30 min at 0 °C, the reaction mixture was quenched by addition of an aqueous saturated solution of NaHCO_3 . The aqueous layer was extracted with CH_2Cl_2 , the combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated. Filtration through a pad of silica gel (hexanes / ethyl acetate = 80/20) followed by HPLC (hexanes / ethyl acetate = 85/15) afforded 22.2

mg (77% from **13**) of **23** as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.33 (d, J = 15.5 Hz, 1H), 6.20 (s, 1H), 5.87 (d, J = 15.5 Hz, 1H), 5.31 (s, 1H), 4.89 (d, J = 6.6 Hz, 1H), 4.74 (d, J = 6.6 Hz, 1H), 4.02 (m, 1H), 3.82 (d, J = 4.2 Hz, 1H), 3.77 (s, 3H), 2.38 (dd, J = 14.9 and 8.6 Hz, 1H), 2.30 (dd, J = 14.9 and 5.6 Hz, 1H), 1.98 (m, 1H), 1.93 (s, 3H), 1.82 (s, 3H), 1.65 (m, 1H), 1.49 (s, 3H), 1.45-1.41 (2H), 1.36-1.24 (5H), 0.97 (t, J = 8.0 Hz, 9H), 0.89 (t, J = 7.0 Hz, 3H), 0.62 (q, J = 8.0 Hz, 6H), 0.12 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 167.9, 153.4, 150.8, 144.0, 133.2, 125.8, 115.8, 89.9, 83.1, 78.8, 75.0, 51.5, 48.6, 40.2, 32.5, 31.8, 26.3, 25.3, 22.6, 21.8, 14.0, 12.9, 7.0, 5.2, 0.0; IR (thin film) 2955, 1724, 1622, 1300, 1250, 1170, 1070, 1020, 840 cm^{-1} ; HRMS (electrospray) for $\text{C}_{31}\text{H}_{58}\text{O}_5\text{Si}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ calcd. 589.3721, found 589.3727; $[\alpha]_{\text{D}}^{25}$ = -20.4 (c 0.93, CHCl_3).

Synthesis of Methyl-(2*E*,4*E*,6*S*,7*S*,8*R*,9*S*)-4,6-dimethyl-6,9-*O*-methylenide-8-(*E*-2'-methyl-3'-iodoprop-2'-enyl)-7-[(triethylsilyl)oxy]-tetradeca-2,4-dienoate (6**):**

To a solution of **23** (13.9 mg, 0.024 mmol) in CH_3CN (0.5 mL) at 0 $^\circ\text{C}$ was added NIS (6.6 mg, 0.03 mmol, 1.2 eq.) in one portion. After 2h at 0 $^\circ\text{C}$, the reaction mixture was quenched by the addition of an aqueous saturated solution of $\text{Na}_2\text{S}_2\text{O}_3$ (3 mL). The aqueous layer was extracted with CH_2Cl_2 , the combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated. Purification of the crude material by preparative thin layer chromatography (hexanes / ethyl acetate = 90/10) gave 13.3 mg (87%) of **6** as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.32 (d, J = 15.7 Hz, 1 H),

6.25 (s, 1 H), 6.00 (s, 1 H), 5.87 (d, $J = 15.7$ Hz, 1 H), 4.87 (A of AB, $J_{AB} = 6.6$ Hz, 1 H), 4.72 (B of AB, $J_{AB} = 6.6$ Hz, 1 H), 3.95 (m, 1 H), 3.76 (s, 3 H), 3.73 (d, $J = 3.6$ Hz, 1 H), 2.52 (A of ABX, $J_{AB} = 14.6$ Hz, $J_{AX} = 8.6$ Hz, 1 H), 2.42 (B of ABX, $J_{AB} = 14.6$ Hz, $J_{BX} = 5.2$ Hz, 1 H), 1.91 (s, 3 H), 1.88 (m, 1H), 1.86 (s, 3 H), 1.64 (m, 1H), 1.48 (s, 3 H), 1.42 (m, 1 H), 1.32-1.25 (m, 6 H), 0.95 (t, $J = 8.0$ Hz, 9 H), 0.89 (t, $J = 6.9$ Hz, 3H), 0.59 (q, $J = 8.0$ Hz, 6 H); ^{13}C NMR (125 MHz, CDCl_3) δ 167.8, 150.5, 146.5, 142.6, 133.9, 116.1, 90.0, 83.2, 78.9, 76.6, 74.9, 51.5, 49.0, 37.9, 32.7, 31.7, 26.2, 26.1, 24.0, 22.6, 14.0, 13.0, 7.0 (3), 5.2 (3); IR (thin film) 3059, 2954, 2932, 2876, 1722, 1623, 1458, 1433, 1377, 1298, 1270, 1170, 1121, 1074, 1019, 841, 726 cm^{-1} ; HRMS (FAB) for $\text{C}_{28}\text{H}_{49}\text{IO}_5\text{SiNa}$ $[\text{M}+\text{Na}]^+$ calcd. 643.2292, found 643.2295; $[\alpha]_D^{24}$ -9.2 ($c = 0.34$, CHCl_3).

Synthesis of Methyl-(6*S*,7*S*,8*R*,9*S*)-4,6-dimethyl-6,9-*O*-methylidene-8-[(1'*E*-3'*E*,5'*S*,6'*R*,7'*R*,8'*R*,9'*R*,10'*R*)-8'-[(*tert*-butyldimethylsilyl)oxy]-10'-[(triethylsilyl)oxy]-6'-hydroxy)-[1',7',9'-trimethyl]-5'-(methoxy)-undeca-1',3'-diene]-7-

[(triethylsilyl)oxy]-icosa-2,4,10,12-tetraenoate (15): The boronic acid **6** (153 mg, 0.30 mmol) and vinyl iodide **5** (157 mg, 0.25 mmol) were combined in 4 mL of degassed THF/H₂O (4 : 1 v : v) and the solution was further degassed via one freeze-pump-thaw cycle. The reaction was treated sequentially with Pd(Ph₃P)₄ (29 mg, 0.025 mmol), and Ti(OEt)₄ (33 μL , 0.45 mmol) and the mixture stirred at 23 °C. After 75 min, additional Pd(Ph₃P)₄ (10 mg, 0.009 mmol), and Ti(OEt)₄ (10 μL , 0.13 mmol) were added and the

reaction stirred for an additional 15 min, at which time TLC analysis indicated the reaction was complete. The reaction mixture was diluted with Et₂O/hexanes (1 : 1), filtered through Celite to remove salts, and the residue concentrated. Purification of this crude product by column chromatography (15 g SiO₂, 5% –10% EtOAc/hexanes) provided 206 mg (85%) of **15**. ¹H NMR (CDCl₃, 500 MHz) δ 7.26 (d, *J* = 14.3 Hz, 1H), 6.45 (dd, *J* = 15.1, 10.7 Hz, 1H), 6.21 (s, 1H), 5.99 (d, *J* = 10.7 Hz, 1H), 5.83 (d, *J* = 15.6 Hz, 1H), 5.56 (dd, *J* = 15.1, 8.1 Hz, 1H), 4.91 (A of AB, *J* = 6.5 Hz, 1H), 4.76 (B of AB, *J* = 6.5 Hz, 1H), 4.00 (dd, *J* = 9.2, 2.00 Hz, 1H), 3.92 (d, *J* = 8.1 Hz, 1H), 3.82 to 3.72 (m, 3H), 3.75 (s, 3H), 3.49, (app. t, *J* = 8.1 Hz, 1H), 3.35 (s, 1H), 3.25 (s, 3H), 2.34 (dd, *J* = 14.4, 8.8 Hz, 1H), 2.24 (dd, *J* = 14.4, 4.6 Hz, 1H), 2.01 to 1.95 (m, 1H), 1.93 to 1.80 (m, 2H), 1.91 (s, 3H), 1.79 (s, 3H), 1.70 to 1.60 (m, 1H), 1.51 (s, 3H), 1.48 to 1.38 (m, 1H), 1.38 to 1.20 (m, 6H), 1.05 (d, *J* = 6.1 Hz, 3H), 1.01 (d, *J* = 7.1 Hz, 3H), 0.99 to 0.85 (m, 18H), 0.89 (s, 12H), 0.88 (t, *J* = 3.2 Hz, 3H), 0.64 to 0.55 (m, 12H), 0.10 (s, 3H), 0.08 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 167.9, 150.7, 143.7, 137.1, 133.4, 130.6, 129.8, 126.7, 115.8, 89.9, 83.2, 82.3, 79.5, 78.8, 77.2, 74.9, 73.5, 70.1, 55.9, 51.5, 49.1, 44.3, 37.6, 37.6, 32.8, 31.7, 26.2, 25.5, 22.6, 19.9, 18.3, 16.9, 14.0, 12.9, 11.7, 11.6, 7.0, 6.9, 5.2, -3.5, -3.7; IR (neat) 2956, 2878, 1724, 1623, 1463, 1298, 1253, 1170, 1075, 1017, 837, 774, 742 cm⁻¹; HRMS (FAB+) for C₅₂H₁₀₀O₉NaSi₃ [M+Na]⁺ calcd. 975.6573, found 975.6527; [α]_D²⁶ –21.2 (*c* 0.92, CHCl₃).

Synthesis of (1*S*,2*E*,4*E*,8*R*,9*S*,10*E*,12*E*,15*R*,16*S*,20*S*)-8-[(1'*R*,2'*R*,3'*S*,6'*R*,7'*S*,8'*R*)-2',7'-[di(*tert*-Butyldimethylsilyl)oxy]-4'-[(triethylsilyl)oxy]-(1',3',dimethyl)-pentyl]-20-[(triethylsilyl)oxy]-9-methoxy-1,3,13-trimethyl-16-pentyl-7,17,19-trioxabicyclo[13.4.1]eicosa-2,4,10,12-tetraene-6-one (16): To the ester **15** (130 mg, 0.14 mmol) in 5.5 mL of Et₂O/THF (10 : 1) was added KOSi(Me)₃ (39 mg, 0.30 mmol), and the mixture stirred for 24 h. The reaction was diluted with EtOAc (25 mL) and H₂O (5 mL), and the biphasic mixture stirred vigorously for 5 min. The organic layer was separated and the aqueous was made acidic by the addition of 1N HCl (500 µL), and further extracted with EtOAc. The combined organic solution was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to provide 126 mg of the crude acid which was used without further purification.

The crude acid (126 mg, 0.14 mmol) was azeotropically dried by concentration from benzene (3x) on a rotary evaporator. The residue was dissolved in 3 mL of THF and treated sequentially with *i*-Pr₂NEt (356 µL, 2.1 mmol) and 2,4,6-trichlorobenzoylchloride (TCBC) 174 µL, 1.1 mmol), and the reaction stirred at 23 °C for 2 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in 1.5 mL of toluene, and added to a solution of 4-dimethylaminopyridine (DMAP) (166 mg 1.36 mmol), followed by 2 mL of toluene rinse. The reaction was heated to reflux for 13 h, cooled to 23 °C and filtered. The filtrate was diluted with Et₂O and washed with H₂O, brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (10 g of Davisil, 2% - 5% EtOAc/hexanes) followed by HPLC (21 mm column, 5% EtOAc/hexanes) to provide 78 mg (62%) of **16**. ¹H NMR (CDCl₃, 500 MHz) δ 7.10 (d, *J* = 15.6 Hz, 1H), 6.49 (dd, *J* = 14.9, 10.7 Hz, 1H), 5.8 (d, *J* = 10.7 Hz, 1H), 5.70 (d, *J* = 15.8 Hz, 1H) 5.65 (s, 1H), 5.22 (dd, *J* = 14.9, 8.6 Hz, 1H), 5.02 (dd, *J* = 7.6, 4.6 Hz, 1H), 4.76 (d, *J* = 8.8 Hz, 1H), 4.68 (d, *J* = 8.8 Hz, 1H), 3.96 (app. t, *J* = 3.4 Hz, 1H), 3.88 (app. t, *J* = 8.1 Hz, 1H), 3.83 (app t, *J* = 6.4 Hz, 1H), 3.79 (d, *J* = 7.3 Hz, 1H), 3.64 to 3.58 (m, 1H), 3.24 (s, 3H), 2.67 (dd, *J* = 7.3, 6.9 Hz, 1H), 2.09 to 2.02

(m, 1H), 1.99 (dd, $J = 9.0, 4.9$ Hz, 1H), 1.96 (s, 3H), 1.95 (d, $J = 8.3$, 1H), 1.92 to 1.85 (m, 1H), 1.86 (s, 3H), 1.65 to 1.55 (m, 1H), 1.40 to 1.20 (m, 7H), 1.39 (s, 3H), 1.10 (d, $J = 6.4$ Hz, 3H), 1.02 (t, $J = 8.1$ Hz, 12H), 0.95 (t, $J = 7.8$ Hz, 9H), 0.88 (t, $J = 3.4$ Hz, 3H), 0.88 (s, 12H), 0.81 to 0.69 (m, 6H), 0.61 (q, $J = 7.8$ Hz, 6H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 166.7, 150.8, 142.2, 141.2, 134.4, 131.6, 128.2, 125.1, 116.5, 86.4, 85.4, 81.2, 78.6, 75.5, 74.9, 73.2, 70.3, 55.7, 47.4, 43.1, 42.6, 34.2, 31.9, 30.2, 26.1, 25.9, 25.5, 22.6, 20.1, 20.0, 18.5, 14.1, 12.0, 11.5, 10.2, 7.3, 7.1, 5.7, 5.3, -3.6, -4.1; IR (neat) 2957, 2878, 1713, 1461, 1373, 1253, 1089, 1018, 967, 869, 835, 773, 736, 674 cm^{-1} ; HRMS (FAB+) for $\text{C}_{51}\text{H}_{58}\text{O}_4\text{NaSi}_3$ $[\text{M}+\text{Na}]^+$ calcd. 943.6310, found 943.6318; $[\alpha]_D^{26} -2.3$ (c 0.78, CHCl_3).

Synthesis of (1*S*,2*E*,4*E*,8*R*,9*S*,10*E*,12*E*,15*R*,16*S*,20*S*)-8-[(1'*R*,2'*R*,3'*S*,6'*R*,7'*S*,8'*R*)-2',7'-di(*tert*-Butyldimethylsilyl)oxy-(1',3'-dimethyl)-pent-4'-one]-20-[(trimethylsilyl)oxy]-9-methoxy-1,3,13-trimethyl-16-pentyl-7,17,19-trioxabicyclo[13.4.1]eicosa-2,4,10,12-tetraene-6-one (17). A solution of the macro lactone **16** (78 mg, 0.085 mmol) in THF (2.5 mL) was cooled to 0 °C and a solution of TFA (212 μL , 4.0M in H_2O) was added. The reaction was stirred for 150 min until complete by TLC analysis (20% ethyl acetate/hexanes). The reaction was diluted with 15 mL of Et_2O and washed with NaHCO_3 (3 x 2 mL), dried over MgSO_4 , filtered, and concentrated on the rotary evaporator followed by high vacuum to give 72 mg

(>99%) of crude alcohol which was >95% pure by ^1H -NMR and was used without purification.

A solution of the crude alcohol (72 mg crude, 0.085 mmol) in CH_2Cl_2 (3.0 mL) at 0 °C was treated with pyridine (34 μL , 0.42 mmol), followed by Dess-Martin periodinane (72 mg, 0.17 mmol). The reaction stirred at 0 °C for 2 h. TLC analysis (20% ethyl acetate/hexanes) at this point showed the reaction to be approximately 70% complete. Additional pyridine (68 μL , 0.84 mmol) and Dess-Martin periodinane (72 mg, 0.17 mmol) were added and the reaction stirred until complete by TLC analysis (4 h). The reaction mixture was diluted with Et_2O (20 mL) and washed (3 x 2 mL) with a 1:1 (v:v) mixture of satd. $\text{Na}_2\text{S}_2\text{O}_3$ and satd. NaHCO_3 , dried over MgSO_4 , filtered, and concentrated on the rotary evaporator. The crude residue was purified on a Davisil[®] column (5.0 g) eluted with a gradient of ethyl acetate/hexanes (5–20%) to yield 61 mg (90% from macrolactone **16**) of the methyl ketone **17**: ^1H NMR (CDCl_3 , 500 MHz) δ 7.13 (d, J = 15.9 Hz, 1H), 6.48 (dd, J = 15.1, 11.0 Hz, 1H), 5.78 (d, J = 11.0 Hz, 1H), 5.72 (d, J = 15.9 Hz, 1H), 5.66 (s, 1H), 5.14 (dd, J = 15.1, 9.5 Hz, 1H), 4.91 (dd, J = 7.8, 5.6 Hz, 1H), 4.77 (d, J = 8.5 Hz, 1H), 4.70 (d, J = 8.5 Hz, 1H), 4.30 (app. t, J = 3.7 Hz, 1H), 3.80 (d, J = 7.3 Hz, 1H), 3.70 (d, J = 8.8 Hz, 1H), 3.61 (app. t, J = 7.6 Hz, 1H), 3.19 (s, 3H), 2.95 (ddd, J = 11.0, 10.3, 3.2 Hz, 1H), 2.75 to 2.64 (m, 1H), 2.18, (s, 3H), 2.04 to 1.90 (m, 2H), 1.98 (s, 3H), 1.88 (s, 3H), 1.64 to 1.56 (m, 1H), 1.38 (s, 3H), 1.38 to 1.22 (m, 8H), 1.13 (d, J = 7.1 Hz, 3H), 1.02 (d, J = 7.8 Hz, 3H), 1.00 (t, J = 5.6 Hz, 9H), 0.89 (t, J = 6.8 Hz, 3H), 0.88 (s, 9H), 0.81 to 0.70 (m, 6H), 0.15 (s, 3H), 0.09 (s, 3H) δ 211.8, 166.9, 151.2, 142.7, 141.8, 134.3, 132.1, 127.8, 125.0, 116.1, 86.4, 81.2, 78.6, 75.5, 74.7, 71.8, 55.6, 48.7, 47.4, 43.8, 34.2, 31.9, 30.2, 29.7, 29.1, 26.0, 25.8, 25.5, 22.6, 20.2, 18.3, 14.1, 12.5, 12.0, 11.0, 7.3, 5.7, -4.2, -4.3; IR (thin film, CHCl_3) 2956, 2930, 2878, 2857, 1709, 1462, 1369, 1359, 1252, 1173, 1089, 1024, 869, 829, 774, 738 cm^{-1} ; HRMS (electrospray) for $\text{C}_{45}\text{H}_{80}\text{O}_8\text{Si}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ calcd. 827.5289, found 827.5301; $[\alpha]_D^{23}$ +13.4 (c 1.65, CHCl_3).

Synthesis of (1*S*,2*E*,4*E*,8*R*,9*S*,10*E*,12*E*,15*R*,16*S*,20*S*)-8-[(1'*R*,2'*R*,3'*S*,6'*R*,7'*S*,8'*R*)-2',7'-di(*tert*-Butyldimethylsilyl)oxy-(1',3',7'-trimethyl)-non-4'-one]-20-[(trimethylsilyl)oxy]-9-methoxy-1,3,13-trimethyl-16-pentyl-7,17,19-trioxabicyclo[13.4.1]eicosa-2,4,10,12-tetraene-6-one (18): A solution of the methyl ketone **17** (21.5 mg, 0.027 mmol) in THF was cooled to –78 °C and treated with a 1:1 (v:v) mixture of Et₃N and TMS-Cl (70 μL, 0.27 mmol), stirred for 10 min and then treated with LiHMDS (1.0M in THF, 70 μL). The solution was stirred for 30 min and then quenched by the addition of cold pH 7 buffer then extracted with 1:1 Et₂O/pentane. The organic extracts were dried over Na₂SO₄, filtered and concentrated to give 22.4 mg of the crude enol silane, which was used in the next reaction without purification.

Freshly prepared aldehyde **3** (57 mg, 0.27 mmol) was azeotropically dried by concentrating with benzene (2X). A solution of the crude enol ether in benzene was then added to the aldehyde and the solution concentrated to dryness on the rotary evaporator followed by high vacuum (3 min). The residue was redissolved in CH₂Cl₂ (100 μL) and 4Å mol sieves (18 mg) were added. The solution stirred for 10 min then cooled to –78 °C. A solution of BF₃•Et₂O (80 μL, 3.0 M in CH₂Cl₂) was added slowly down the side of the flask to allow cooling of the reagent. The reaction was stirred at –78 °C for 40 min and then quenched by the addition of NaHCO₃. The mixture was extracted with Et₂O and the extracts were dried over MgSO₄, filtered, and concentrated on the rotary evaporator

followed by high vacuum. The residue was purified by column chromatography (5g of SiO₂ 5% to 10 % EtOAc/hexanes) to provide 23 mg of the desired Felkin aldol that contained 10% of unreacted methyl ketone. HPLC (20 mm column, 10% ethyl acetate/hexanes) purification of this material then provided 19.6 mg (72%, 80% based on recovered methyl ketone) of the desired Felkin aldol **18** as well as 0.4 mg of the anti-Felkin aldol diastereomer: ¹H NMR (C₆H₆, 500 MHz) δ 7.40, (d, *J* = 16.7 Hz, 1H), 6.64, (dd, *J* = 14.9, 10.7 Hz, 1H), 5.92, (d, *J* = 16.7 Hz, 1H), 5.80, (d, *J* = 10.7 Hz, 1H), 5.77, (s, 1H), 5.43, (dd, *J* = 15.1, 9.3 Hz, 1H), 5.42, (dd, *J* = 8.3, 8.0 Hz, 1H), 4.81, (ddd, *J* = 9.3, 5.1, 2.4 Hz, 1H), 4.73, (d, *J* = 8.5 Hz, 1H), 4.68 (dd, *J* = 4.6, 3.2 Hz, 1H), 4.42 (A of AB, *J*_{AB} = 8.6 Hz, 1H), 3.95, (B of AB, *J*_{AB} = 8.6 Hz, 1H), 3.90 – 3.82, (M, 2H), 3.54, (dd, *J* = 9.0, 6.6 Hz, 1H), 3.32, (d, *J* = 2.2 Hz, 1H), 3.21, (s, 3H), 3.18 – 3.10, (m, 1H), 2.84, (A of ABX, *J*_{AB} = 17.1 Hz, *J*_{AX} = 9.5 Hz, 1H), 2.66, (app. q, *J* = 7.3 Hz, 1H), 2.56, (B of ABX, *J*_{AB} = 17.1 Hz, *J*_{BX} = 2.9 Hz, 1H), 2.34 – 2.26, (m, 1H), 1.99, (s, 3H), 1.92 – 1.80, (m, 3H), 1.72, (s, 3H), 1.60 – 1.50, (m, 1H), 1.46 (s, 3H), 1.42 – 1.30, (m, 7H), 1.24 (d, *J* = 7.3 Hz, 3H), 1.18, (d, *J* = 7.1 Hz, 3H), 1.16, (d, *J* = 6.1 Hz, 3H), 1.08, (s, 9H), 0.99, (d, *J* = 7.1 Hz, 3H), 0.96, (s, 9H), 0.92, (s, 9H), 0.92, (t, *J* = 8.1 Hz, 3H), 0.70 – 0.58, (m, 6H), 0.34 (s, 3H), 0.29, (s, 3H), 0.12, (s, 3H), 0.04, (s, 3H); ¹³C NMR (C₆H₆, 125 MHz) δ 213.5, 166.8, 151.0, 142.5, 141.7, 134.7, 132.3, 129.0, 125.8, 116.9, 86.9, 86.6, 81.2, 78.5, 75.8, 75.1, 72.5, 71.9, 66.5, 55.7, 49.2, 47.8, 47.0, 44.9, 44.2, 34.5, 32.2, 30.6, 26.4, 26.2, 26.0, 25.8, 23.0, 21.9, 20.3, 18.7, 18.1, 14.3, 12.6, 12.0, 11.1, 10.5, 7.4, 6.0, -3.8, -4.0, -4.3, -4.9; IR (thin film, benzene) 2965, 1710, 1460, 1376, 1254, 1087, 1022, 836, 775, 737, cm⁻¹; HRMS (electrospray) for C₅₆H₁₀₄O₁₀Si₃Na [M+Na]⁺ calcd. 1043.6835, found 1043.6838; [α]_D²⁶ +18.8 (c 0.98, benzene).

Synthesis of (1*S*,2*E*,4*E*,8*R*,9*S*,10*E*,12*E*,15*R*,16*S*,20*S*)-8-[(1'*R*,2'*R*,3'*S*,6'*R*,7'*S*,8'*R*)-3'-(2''*R*,4''*R*,5''*R*,6''*S*)-(2'',dihydroxy-5'',6''-dimethyl-tetrahydropyran-2''-yl)-2'-hydroxy-1'-methylbutyl]-20-hydroxy-9-methoxy-1,3,13-trimethyl-16-pentyl-7,17,19-trioxabicyclo[13.4.1]eicosa-2,4,10,12-tetraene-6-one (Formamycin Aglycon) (19): A solution of TAS-F (9.7mg, 0.035 mmol,) and H₂O (1.4 μL, 0.078 mmol,) in DMF (100 μL) was added to a solution of **18** (3.6 mg, 0.0035 mmol) in DMF (50 μL). The reaction stirred for two hours until only one lower R_f spot (R_f = 0.25) was present by TLC analysis (50% ethyl acetate/hexanes). The reaction was concentrated to approx. 50 μL and then loaded directly onto a Davisil[®] column (3.0 g) and eluted with a gradient of ethyl acetate/hexanes (25–50%) to yield 2.4 mg of a crude white solid which was further purified on HPLC (10mm column, 60% EA/hex) to furnish 1.9 mg (80%) of the formamycin aglycon **19** a white solid: ¹H NMR (4 : 1 CDCl₃/C₆H₆, 500 MHz) δ 7.22, (d, *J* = 15.6 Hz, 1H), 6.48, (dd, *J* = 14.9, 10.7 Hz, 1H) 5.71 (d, *J* = 11.0 Hz, 1H), 5.68 (s, 1H), 5.65, (d, *J* = 15.9 Hz, 1H), 5.64, (d, *J* = 1.2 Hz, 1H), 5.15 (dd, *J* = 14.9, 9.5 Hz, 1H), 4.91, (d, *J* = 9.0 Hz, 1H), 4.78, (d, *J* = 4.1 Hz, 1H), 4.68, (A of AB, *J*_{AB} = 8.7 Hz, 1H), 4.58, (B of AB, *J*_{AB} = 8.7 Hz, 1H), 4.14, (m, *J* = 10.7, 2.7 Hz, 1H), 3.86, (app. t, *J* = 9.0 Hz, 1H), 3.70, (m, *J* = 12.5, 10.0, 6.1 Hz, 1H), 3.63, (m, 1H), 3.56, (app. t, *J* = 7.3 Hz, 1H), 3.51, (dd, *J* = 8.3, 5.6 Hz, 1H), 3.18, (s, 3H), 2.60, (app. q, *J* = 9.3 Hz, 1H), 2.24, (dd, *J* = 12.0, 4.6 Hz, 1H), 2.14, (ddd, *J* = 13.9, 10.7, 7.1 Hz, 1H), 1.92, (d, *J* = 14.1 Hz, 1H), 1.88, (s, 3H), 1.80 – 1.73 (m, 1H), 1.77, (s, 3H), 1.69, (app. q, *J* = 7.1 Hz), 1.62 – 1.52, (m, 1H), 1.44, (d, *J* = 5.6 Hz, 1H), 1.30 – 1.18 (m, 8H), 1.28, (s, 3H), 1.09, (d, *J* = 6.4 Hz, 1H), 1.07, (m, 1H), 1.01, (d, *J* = 7.1, Hz, 1H), 0.89, (d, *J* = 6.6

Hz, 1H), 0.86, (d, $J = 6.8$ Hz, 1H), 0.78 (d, $J = 6.8$ Hz, 1H); ^{13}C NMR (4 : 1 $\text{CDCl}_3/\text{C}_6\text{H}_6$, 125 MHz) δ 169.5, 153.6, 143.2, 142.5, 134.6, 132.7, 127.4, 125.3, 114.9, 99.3, 86.4, 82.2, 80.0, 77.8, 75.8, 74.8, 70.4, 70.3, 69.2, 55.6, 47.1, 45.9, 43.4, 41.7, 37.2, 34.7, 32.0, 30.1, 25.7, 24.9, 22.7, 20.1, 19.3, 14.1, 12.9, 11.6, 9.7, 7.1; IR (thin film, benzene) 3419, 2929, 1682, 1455, 1260, 1150, 1087, 1037, 968, 899, 847, 808, 678 cm^{-1} ; HRMS (FAB) for $\text{C}_{38}\text{H}_{62}\text{O}_{10}\text{Na}$ $[\text{M}+\text{Na}]^+$ calcd. 701.4241, found 701.4244; $[\alpha]_{\text{D}}^{26} +12.1$ (c 0.19, benzene).

STEREOCHEMICAL ASSIGNMENTS FOR COMPOUNDS **9** AND **22**

Aldol **7** was converted to the β -methoxymethoxy Weinreb amide **24** in 2 steps (73%). Displacement of the amide moiety by α -ethoxyvinyl lithium in THF, followed by non-selective reduction of the ketone function afforded a 1/1 mixture of **9-syn** and **9-anti**. Formation of the cyclic acetal **26** was effected by treatment with Me_2BBr and 2,6-DTMB. NOe experiments on the acetal derived from **9-syn** were not conclusive. However, nOe enhancements were observed for **26** (derived from **9-anti**) between the C(1) and acetal proton, C(4) and C(5) proton as well as C(5) and acetal proton, indicating an *anti* relationship between C(3) and (C4) proton and a *syn* relationship between C(4) and C(5) proton. By deduction, compound **9-syn** possess a *syn,syn* relationship between the C(3), C(4) and C(5) stereocenters.

DDQ oxidation of the PMB ether **22** gave the p-methoxylidene (PMP) acetal **28**. Semi-hydrogenation of the triple bond with H_2 and Lindlar's catalyst afforded **29**. Key ^1H nOe enhancements were observed between the C(3), C(5) and acetal methine proton, indicating a *syn* relationship for the C(4)-C(5) hydroxyl functions in **22**.

Table 1: ¹H-NMR and ¹³C-NMR Data of formamycin and formamycin aglycon.

Position	Formamycin	¹³ C-NMR Formamycin aglycon	Difference	Formamycin	¹ H-NMR Formamycin Aglycon	Difference
1	169.6	169.5	0.1			0.00
2	115.0	114.9	0.1	5.69	5.65	0.04
3	153.8	153.6	0.2	7.27	7.22	0.05
4	134.6	134.6	0.0			0.00
5	142.6	142.5	0.1	5.71	5.68	0.03
6	80.0	80.0	0.0			0.00
7	74.8	74.8	0.0	3.56	3.51	0.05
				1.66	1.58	0.08
8	47.2	47.1	0.1	2.65	2.60	0.05
9	34.8	34.7	0.1	1.83	1.78	0.05
				1.97	1.92	0.05
10	143.4	143.2	0.2			0.00
11	125.3	125.3	0.0	5.76	5.71	0.05
12	132.9	132.7	0.2	6.53	6.48	0.05
13	127.8	127.4	0.4	5.20	5.15	0.05
14	82.3	82.2	0.1	3.91	3.86	0.05
15	75.8	75.8	0.0	4.96	4.91	0.05
16	37.3	37.2	0.1	2.19	2.14	0.05
17	70.5	70.4	0.1	4.20	4.14	0.06
			0.0	4.87	4.78	0.09
18	41.9	41.7	0.2	1.76	1.69	0.07
19	99.4	99.3	0.1	5.71	5.64	0.07
20	40.2	45.9	-5.7	1.17	1.07	0.10
				2.34	2.24	0.10
21	76.2	69.2	7.0	3.81	3.63	0.18
			0.0		1.44	21(OH)
22 ^a	43.7	43.4	0.3	1.20-1.35	1.18-1.30	0.04
23	69.8	70.3	-0.5	3.78	3.70	0.08
24	19.5	19.3	0.2	1.15	1.09	0.06
25	78.0	77.8	0.2	3.61	3.56	0.05
26 ^a	30.2	30.1	0.1	1.20-1.35	1.18-1.30	0.04
27 ^a	25.8	25.7	0.1	1.20-1.35	1.18-1.30	0.04
28 ^a	32.0	32.0	0.0	1.20-1.35	1.18-1.30	0.04
29 ^a	22.8	22.7	0.1	1.20-1.35	1.18-1.30	0.04
30	14.2	14.1	0.1	0.91	0.86	0.05
31	11.7	11.6	0.1	1.83	1.77	0.06
32	24.9	24.9	0.0	1.33	1.28	0.05
33	86.5	86.4	0.1	4.63	4.58	0.05
34	20.2	20.1	0.1	1.93	1.88	0.05
35	55.7	55.6	0.1	3.23	3.18	0.05
36	9.7	9.7	0.0	0.83	0.78	0.05
37	7.3	7.1	0.2	1.08	1.01	0.07
38	13.3	12.9	0.4	0.99	0.89	0.10

^a The proton resonances overlapped and could not be resolved.